



Liebeskind, D. S. et al. (2018) eTICI reperfusion: defining success in endovascular stroke therapy. *Journal of NeuroInterventional Surgery*, (doi:10.1136/neurintsurg-2018-014127).

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/167474/>

Deposited on: 23 August 2018

Enlighten – Research publications by members of the University of Glasgow\_  
<http://eprints.gla.ac.uk>

**Abstract**

***Background***

Revascularization after endovascular therapy for acute ischemic stroke is measured by TICI, yet variability exists in scale definitions. We examined the degree of reperfusion with the expanded TICI (eTICI) scale and association with outcomes in the HERMES collaboration of recent endovascular trials.

***Methods***

The HERMES Imaging Core, blind to all other data, evaluated angiography after endovascular therapy in HERMES. A battery of TICI scores (mTICI, TICI, TICI2C) was used to define reperfusion of the initial target occlusion defined by noninvasive imaging and conventional angiography.

***Results***

Angiography of 801 subjects was available, including 797 defined by non-invasive imaging (154 ICA, 583 M1, 60 M2) and 748 by conventional angiography (195 ICA, 459 M1, 94 M2). Among 729 subjects in whom reperfusion grade could be established, using eTICI (3=100%, 2C=90-99%, 2b67=67-89%, 2b50=50-66%) of the conventional angiography target occlusion, there were 63 eTICI 3 (9%), 166 eTICI 2c (23%), 218 eTICI 2b67 (30%), 103 eTICI 2b50 (14%), 100 eTICI 2a (14%), 19 eTICI 1 (3%) and 60 eTICI 0 (8%). mRS shift analyses from baseline to 90 days revealed increasing TICI grades were linked with better outcomes, with significant distinctions between TICI 0/1 vs 2a (p=0.028), 2a vs 2b50 (p=0.017) and 2b50 vs 2b67 (p=0.014).

***Conclusions***

The benefit of endovascular therapy in HERMES was strongly associated with increasing degrees of reperfusion defined by eTICI. The eTICI metric identified meaningful distinctions in clinical outcomes and may be used in future studies and routine practice.

### **Key Words**

Stroke, reperfusion, ischemia, angiography, endovascular therapy

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Endovascular therapy is a highly effective treatment for acute ischemic stroke caused by large artery occlusion in the anterior cerebral circulation, significantly increasing the likelihood of recovery to independence.<sup>1</sup> Reperfusion of the ischemic territory downstream from an arterial occlusion is the therapeutic mechanism responsible for benefit. The extent of reperfusion, however, may vary across individual cases depending on numerous factors, including the degree of collateral circulation.<sup>2-5</sup> Most commonly, reperfusion is evaluated on angiography performed immediately after recanalization or when reopening of the arterial occlusion is achieved.

Several iterations of the Thrombolysis In Cerebral Infarction (TICI) score, adapted from the TIMI coronary circulation scoring system to the cerebral circulation have been used to quantify reperfusion.<sup>6</sup> Successive refinements of the original TICI scale were implemented to enhance standardization for different sites of arterial occlusion and to optimally discern subtle distinctions in the amount of blood flow restored after thrombectomy. Multiple studies have examined the inter-rater reliability of TICI grades and future such analyses are warranted. Variability exists, however, in definitions, nomenclature, use and reporting. Consensus recommendations for angiographic revascularization standards developed in 2013 defined successful reperfusion by a modified TICI (mTICI) score signifying filling of 50% or more of the downstream territory.<sup>7</sup>

Reperfusion of the ischemic territory downstream from an arterial occlusion in stroke is distinct from recanalization, defined as restoring patency in the occluded arterial segment.<sup>8, 9</sup> Reperfusion specifically refers to re-establishing blood flow via normal arterial routes, in contrast to indirect collateral perfusion. The extent of reperfusion is quantified by the percentage of the downstream territory and is therefore dependent on defining the specific site of initial arterial occlusion. Such measurement of reperfusion is most often conducted on biplane

angiography where the three-dimensional nature of the arterial territory must be inferred. Grading the extent of reperfusion or assigning a TICI score is typically conducted by the local operator or treating physician at the end of the procedure. Achieving a favorable TICI grade is considered a quality metric for endovascular stroke therapy. Rating is influenced by local rater experience and central core-lab adjudication is commonly more conservative compared to local ratings. Since the original description of TICI 15 years ago, several intermediate grades of reperfusion have been introduced. The entire range of grade 2 TICI reperfusion, extending from a minimum of any distal branch filling to almost complete downstream perfusion, has been subdivided and confusingly labeled with inconsistent terminology.

Availability of data from reperfusion trials now allows critical review of TICI reperfusion grade definitions. Standardization of TICI grading is essential for clinical practice and for future trials. We examined the relationship of reperfusion grades and clinical outcomes using individual patient data in the Highly Effective Reperfusion Evaluation in Multiple Endovascular Stroke (HERMES) trials that comprise the majority of randomized, controlled trials undertaken with modern endovascular treatments.<sup>10</sup> Data were systematically analyzed by an experienced core lab to delineate TICI reperfusion and substantiate prior scale distinctions with the associated clinical outcomes after stroke treatment.

## Methods

### *Study Design*

HERMES included 7 distinct endovascular therapy trials that established the efficacy of mechanical thrombectomy for acute ischemic stroke. Detailed methodology of each trial has been previously reported.<sup>11-13</sup> Ethics approval was obtained from the local institutional review

board and written informed consent was obtained from patients. In HERMES, the entire imaging and angiography datasets of the 7 participating trials were centrally pooled in the Neurovascular Imaging Research Core. Anonymized images of each enrolled subject were indexed and relabeled by a randomly assigned HERMES subject identification number to mask any possible association with the original randomized controlled trial. In each of the original trials, only the subjects randomized to endovascular therapy underwent angiography. As a result, the HERMES angiography dataset reflects solely those subjects assigned to endovascular therapy.

*Angiography Core Laboratory Evaluation*

The HERMES angiography dataset was analyzed by an independent core laboratory with extensive experience in adjudication of imaging and angiography from numerous multicenter stroke trials and registries. The angiography images were provided to the core lab without any additional information other than the site of the initial target occlusion determined by noninvasive imaging in the original trial. As technical differences in imaging technique, or dynamic changes in occlusion due to recanalization or distal thrombus migration may occur between baseline noninvasive imaging and conventional angiography, reperfusion was graded based on location of the conventional angiography procedure start.

The HERMES angiography core lab performed a quality assessment of the angiography data, denoting availability, adequacy and limiting factors associated with each subject’s data. As TICI reperfusion in the downstream territory is critically contingent on the specific location of the arterial occlusion, it was imperative that a diagnostic run or contrast injection of the occlusion was available at the procedure start to determine the conventional angiography target occlusion location. Similarly, a final run or diagnostic injection of the same arterial territory was

required to determine TICI reperfusion. In addition, the angiography core lab noted when limited data were available, such as the lack of biplane angiography or failure to acquire adequate runs that precluded evaluation of reperfusion. A battery of various TICI scores in this study population (Table 1) was used to define reperfusion of the initial target occlusion on noninvasive imaging and conventional angiography. This 7-point compilation of TICI grades, termed the expanded TICI or eTICI, reflects all previously reported thresholds used to define reperfusion after endovascular stroke therapy. In brief, eTICI grade 0 is equivalent to no reperfusion or 0% filling of the downstream territory; eTICI 1 reflects thrombus reduction without any reperfusion of distal arteries; eTICI 2a is reperfusion in less than half or 1-49% of the territory; eTICI 2b50 is 50-66% reperfusion, exceeding the modified TICI (mTICI) 2B threshold but below the original TICI 2B cutpoint; eTICI 2b67 is 67-89% reperfusion, exceeding TICI but below TICI 2C; eTICI 2c is equivalent to TICI 2C or 90-99% reperfusion; and eTICI 3 is complete or 100% reperfusion, tantamount to TICI 3. Multiple studies have already examined the inter-rater reliability of all the components of the eTICI.<sup>14, 15</sup> In order to define the inter-rater reliability of the distinction between eTICI 2b50 (50-66% reperfusion, mTICI 2B) and eTICI 2b67 (67-89% reperfusion, TICI 2B), a cohort of 52 subjects was rated independently by 2 readers.

### *Statistical Analyses*

Descriptive methods were used to characterize baseline angiographic features, including distributions across categories. For each HERMES subject, the blinded evaluation of the conventional angiography target occlusion location was noted and compared with the initial target occlusion location for each case. Inter-rater reliability was analyzed using a correlation coefficient and Cohen's kappa statistic. The distribution of eTICI scores for the conventional

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

angiography target occlusion was described and analyzed with respect to the key stroke outcome variable of the modified Rankin score (mRS) at 90 days. Graphical analyses were also used to describe the distribution of mRS at day 90 stroke clinical outcomes for each eTICI grade. mRS distribution analyses at day 90 were used to compare clinical outcomes between neighboring eTICI thresholds, with statistical comparisons by Wilcoxon’s rank-sum test for nonparametric analysis. Finally, receiver operating characteristic (ROC) curves were constructed to illustrate the discriminative value of various TICI classification schemes on the mRS outcomes. The ROC results were described by the area under the curve (AUC) statistic and associated p-values computed by the method of DeLong. For all analyses, a two-tailed p-value less than 0.05 was considered statistically significant, without adjustment for multiple testing. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria).



## Results

### *Arterial Occlusions*

Angiography was available in a total of 801 subjects in HERMES, reflecting 801/871 (92%) of patients assigned to the endovascular treatment arms of the 7 participating trials. The target occlusion on non-invasive imaging was located at the ICA in 154 (19%), proximal MCA or M1 in 583 (73%) and M2 arterial segment in 50 (6%), and on conventional angiography at the ICA in 195 (24%), proximal MCA or M1 in 459 (57%) and M2 arterial segment in 94 (12%).

### *Extent of Reperfusion on eTICI*

The extent of reperfusion was distributed across the entire range of the eTICI scale, including the spectrum from absolutely no reperfusion to complete restoration of flow in the territory downstream of the conventional angiography target occlusion. Among the 801 subjects noted above, reperfusion grade could not be established due to imaging limitations in 72, giving 729 evaluable eTICI scores. No reperfusion or eTICI 0 was noted in 60 (8%) and only reduction in thrombus without filling of distal arterial branches or eTICI 1 in 19 (3%). Reperfusion in less than half the territory or eTICI 2a was noted in 100 (14%). Reperfusion in 50-66% of the territory or eTICI 2b50, equivalent to mTICI 2B yet less than TICI 2B, was noted in 103 (14%). Restoration of flow in 67-89% of the territory or eTICI 2b67, above the TICI 2B threshold yet less than TICI 2C, occurred in 218 (30%). Extensive reperfusion between 90-99%, or eTICI 2c equivalent to TICI 2C, was noted in 166 (23%). Finally, complete or full reperfusion of eTICI 3, equivalent to TICI 3, was found in only 63 (9%).

The distinctions between individual eTICI grades and the resultant discriminant ability of these perfusion categories was critically dependent on the availability of adequate angiographic

views. Diagnostic confidence or potential limitations in the separation of eTICI categories was documented in 25/729 (3%) of subjects. The most common difficulty (n=12) occurred at the intermediate eTICI grades that demarcated eTICI 2b50 from eTICI 2b67, demarcating reperfusion thresholds around the 67% level (Figure 1). Interestingly, the subtle distinction of eTICI 2c and 3, discriminating the TICI 2C (90-99%) category from full or TICI 3 (100%) categories (Figure 2) occurred in only 8/729 (1%) with difficulties between 2b67 and 2c in the remaining 5 cases. Within the eTICI 2c or TICI 2C category, overt distal emboli manifest as vessel cutoffs or menisci were visualized in 67/166 (40%).

Inter-rater reliability for the distinction between eTICI 2b50 and 2b67 (mTICI 2B versus TICI 2B) revealed an agreement of 92% (48/52), with a Cohen's kappa statistic of  $k=0.83$ ,  $p<0.001$ .

*Relationship of eTICI Reperfusion and Clinical Outcomes*

More extensive eTICI reperfusion was associated with better outcomes. Graphical depictions of this relationship for subsets of ICA and M1 MCA occlusions are illustrated in Figure 3. There was an unequivocal, graded pattern of increased proportion of subjects with no or minimal disability (mRS 0-1) hierarchically linked with higher eTICI grades. Similarly, the proportion of severe disability or death (mRS 5-6) was less with higher eTICI grades. Interestingly, even intermediate levels of disability (mRS 2-4) exhibited a clear relationship of decreasing disability with more extensive reperfusion. It should be noted, however, that across almost all eTICI reperfusion grades, there was still a broad distribution of mRS day 90 clinical outcomes.

Direct comparison of the distribution in clinical outcomes of individual, neighboring eTICI grades revealed specific differences between reperfusion categories (Table 2). The relatively small number of subjects with extremely limited (eTICI 0-1) or complete (eTICI 3) reperfusion may have limited such distinctions between eTICI categories at the extreme ends of the scale, whereas differences between intermediate categories of reperfusion were more apparent. The distribution of clinical outcomes was clearly different between eTICI grades 0/1 versus 2a, 2a versus 2b50, and 2b50 versus 2b67 that demarcate the extent of reperfusion at any versus none, 50%, and the 67% thresholds, respectively.

Multivariable modeling of mRS shift on eTICI with covariate adjustment demonstrates that eTICI is an independent predictor of outcome in the presence of covariate adjustment, and more importantly, that adjacent categories 2a/2b50/2b67 are important distinctions (Table 3).

ROC curve analyses (Figure 4) showed similar performance of TICI (AUC 0.657), TICI 2C (AUC 0.661) and eTICI (AUC 0.664) in discriminating better clinical outcomes. All three of these were statistically superior to the mTICI AUC (0.634) ( $p=0.013$  for eTICI vs mTICI in particular).

## Discussion

Our study demonstrates that grades of better reperfusion are incrementally associated with better clinical outcomes. This study is novel as HERMES is a large and ideal dataset to examine TICI grading as it relates to clinical outcomes, pooling many of the large, landmark trials in endovascular therapy. The use of all previously described TICI variants demonstrates the utility of using an expanded or eTICI scale that encompasses these prior scale definitions. We also demonstrated that these eTICI grades are linked with subsequent clinical outcomes after

stroke therapy, providing a cogent rationale for future adoption and largescale use of eTICI. However, while more extensive reperfusion is associated with better clinical outcomes, a wide range of outcomes was evident even at the extremes of poor and full reperfusion, indicating that additional factors remain important determinants of outcome. Previous reports have demonstrated better outcomes with more extensive reperfusion, yet application of all TICI grades and their relative impact on outcomes from HERMES provides important data for the literature.<sup>16, 17</sup>

We confirmed a predominance of M1 occlusions with considerably fewer ICA or M2 occlusions, as reported in individual trials and in previous pooled analyses. We noted that the target occlusion defined on conventional angiography at procedure start differed from that on baseline noninvasive imaging. This may result from interval recanalization or thrombus migration, or alternatively be ascribed to technical differences in acquisition of non-invasive versus invasive imaging techniques. Based on the conventional angiography target occlusion site determined by our HERMES core lab, we corroborate the reperfusion rates reported in the original trial reports, exhibiting substantial predominance of flow restoration to much of the ischemic territory. Importantly, however, the proportion of complete or full reperfusion was substantially less than originally described. There were key distinctions in reperfusion categories when specific thresholds were used to subdivide the ischemic territory. Established consensus recommendations for angiographic standards in endovascular therapy have defined successful reperfusion as exceeding 50% of the territory.<sup>7</sup> We have demonstrated, however, that within the >50% reperfusion category, a considerable number of cases fell into previously-defined finer subdivisions of 50-66%, 67-89% and 90-99%, and that these refinements identify meaningful differences in clinical outcomes.

Our use of all previously defined TICI categories, redefined as eTICI grades, demonstrated that such categories identify gradation of outcomes associated with the extent of reperfusion. Comparison of adjacent or ordinal reperfusion grades on the eTICI scale showed that clinical outcomes vary between each grade, with more pronounced differences within intermediate eTICI categories. Prior studies have provided preliminary evidence that, compared with less granular TICI scales, the more fine-grained TICI scales have added prognostic value and clinical utility.<sup>18-22</sup> The prior studies have been relatively small and with limited geographic scope, limiting their precision and generalizability. We therefore undertook the current study to validate and quantify the superiority of the eTICI in the large, multinational HERMES data set. We have extended previous reports concerning inter-rater reliability of eTICI cutpoints by demonstrating excellent reliability for distinguishing eTICI 2b50 and 2b67 (mTICI 2B versus TICI 2B).<sup>14, 15</sup> This distinction between eTICI 2b50 and 2b67 may be difficult to discern, unlike or more so than other category distinctions (e.g. 2a v. 2b50; 2b67 v. 2c; 2c v. 3). Furthermore, these other category distinctions have been addressed in prior publications, hence it was important to demonstrate inter-rater reliability in this subset. Our results also indicate that this eTICI category distinction is the most significant as it relates to different subsequent clinical outcomes.

Although this analysis establishes that the 7-point eTICI scale predicts increasingly better clinical outcomes, it is important to note that even at the extreme ends of the scale a wide distribution of outcomes may be evident. For example, not all subjects with eTICI 0/1 reperfusion have poor clinical outcomes and conversely, there are subsets of patients with eTICI 2c or 3 reperfusion with outcomes of severe disability or death. Such examples suggest that angiographic outcomes alone have limited utility for clinical outcome prediction. The AUC

1  
2  
3 values for predicting good clinical outcomes were higher for eTICI 2b67 or 2c (>66% or >90%,  
4  
5 respectively) compared with eTICI 3 (>50%), yet such AUC values of 0.66 are relatively  
6  
7 modest, at best. Factors beyond reperfusion, including the underlying pathophysiology such as  
8  
9 extent of established tissue injury, or collateral circulation, clinical variables, or subsequent  
10  
11 events, such as recurrent stroke or hemorrhage, likely influence clinical outcomes. It also  
12  
13 remains unclear whether the cause of limited reperfusion, due to distal emboli or increased  
14  
15 downstream resistance, have different impact in clinical outcomes, even when reperfusion is  
16  
17 almost complete as in eTICI 2c or TICI 2C flow.  
18  
19  
20

21  
22 Limitations of our systematic angiographic evaluation in HERMES include the  
23  
24 availability of adequate images, already restricted to subjects in the endovascular arm of these  
25  
26 randomized, controlled trials. There are numerous aspects of angiography that we may not have  
27  
28 been able to elucidate in this overall or primary paper on eTICI reperfusion in HERMES. Many  
29  
30 of such limitations and data considerations have been addressed in the vast experience of the  
31  
32 IMS I-III trials.<sup>4, 23-25</sup> Evaluation of reperfusion may have been limited by incomplete depiction  
33  
34 of the conventional angiography target occlusion or final diagnostic runs with biplane  
35  
36 angiography. Aside from potentially missing data, variations in technique or local practice may  
37  
38 have precluded adequate visualization of key angiography data. The degree of reperfusion and  
39  
40 clinical outcomes may vary by location of occlusion site and availability of data may be limited  
41  
42 even for ICA versus M1 MCA occlusions (Figure 3). For ICA occlusions, the role of the  
43  
44 ipsilateral ACA and collateral flow may be handled differently with respect to subsequent  
45  
46 reperfusion grading.<sup>24, 25</sup> In our analyses, most of the ICA occlusions did not have any pre-  
47  
48 treatment DSA information on collaterals. As a result, we defined eTICI for ICA lesions without  
49  
50 accounting for potential collateral flow – we scored all based on the ICA lesion being  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 responsible for the ipsilateral ACA and MCA territories. It is agreed that this scenario could be  
4  
5 further addressed by a new scoring system in the future. We did not account for the time required  
6  
7 to achieve final eTICI reperfusion or consider local factors that may have influenced the duration  
8  
9 of the procedure.<sup>26</sup> Such challenges in blinded readings may not capture subtle aspects apparent  
10  
11 at the time of intervention. Importantly, it remains unclear how the angiography was used in real-  
12  
13 time to decide how far to continue with revascularization. The endpoints of successful  
14  
15 reperfusion or the need to continue may have varied widely from operator to operator.  
16  
17 Furthermore, lack of additional clinical demographics and medical history (e.g. atrial fibrillation,  
18  
19 atherosclerosis, other risk factors) beyond those noted in the multivariable model in Table 3 limit  
20  
21 our analyses. In addition, wider application of any rating scale requires ongoing examination.  
22  
23  
24  
25

26 In sum, the benefit of endovascular therapy in HERMES was strongly associated with  
27  
28 increasing degrees of eTICI reperfusion. The eTICI scale reveals important distinctions in the  
29  
30 degree of reperfusion with respect to clinical outcomes, underscoring the need to implement  
31  
32 standard methodology for reporting of angiography in stroke treatment in trials and routine  
33  
34 practice. eTICI provides granularity in distinguishing the extent of reperfusion that is clinically  
35  
36 meaningful. Defining successful reperfusion should be linked with good clinical outcomes,  
37  
38 making it unlikely that a single threshold of eTICI reperfusion will work in all cases. Our  
39  
40 analyses suggest that if a dichotomous threshold were to be used for the definition of successful  
41  
42 reperfusion, then eTICI 2b67, equivalent to TICI 2B, is optimal.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

References

1. Muir KW and White P. HERMES: messenger for stroke interventional treatment. *Lancet*. 2016;387:1695-7.

2. Liebeskind DS. Collateral circulation. *Stroke*. 2003;34:2279-84.

3. Liebeskind DS, Jahan R, Nogueira RG, Zaidat OO, Saver JL and Investigators S. Impact of collaterals on successful revascularization in Solitaire FR with the intention for thrombectomy. *Stroke*. 2014;45:2036-40.

4. Liebeskind DS, Tomsick TA, Foster LD, Yeatts SD, Carrozzella J, Demchuk AM, Jovin TG, Khatri P, von Kummer R, Sugg RM, Zaidat OO, Hussain SI, Goyal M, Menon BK, Al Ali F, Yan B, Palesch YY, Broderick JP and Investigators II. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. *Stroke*. 2014;45:759-64.

5. Singer OC, Berkefeld J, Nolte CH, Bohner G, Reich A, Wiesmann M, Groeschel K, Boor S, Neumann-Haefelin T, Hofmann E, Stoll A, Bormann A and Liebeskind DS. Collateral vessels in proximal middle cerebral artery occlusion: the ENDOSTROKE study. *Radiology*. 2015;274:851-8.

6. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, Dillon W, Warach S, Broderick J, Tilley B, Sacks D, Technology Assessment Committee of the American Society of I, Therapeutic N and Technology Assessment Committee of the Society of Interventional R. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke*. 2003;34:e109-37.

7. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, Marks MP, Prabhakaran S, Kallmes DF, Fitzsimmons BF, Mocco J, Wardlaw JM, Barnwell SL, Jovin TG, Linfante I, Siddiqui AH, Alexander MJ, Hirsch JA, Wintermark M, Albers G, Woo HH, Heck



DV, Lev M, Aviv R, Hacke W, Warach S, Broderick J, Derdeyn CP, Furlan A, Nogueira RG, Yavagal DR, Goyal M, Demchuk AM, Bendszus M, Liebeskind DS, Cerebral Angiographic Revascularization Grading C, group SRw and Force STiCIT. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. 2013;44:2650-63.

8. Zhang JH, Obenaus A, Liebeskind DS, Tang J, Hartman R and Pearce WJ. Recanalization, reperfusion, and recirculation in stroke. *J Cereb Blood Flow Metab*. 2017;37:3818-3823.

9. Schmitz ML, Yeatts SD, Tomsick TA, Liebeskind DS, Vagal A, Broderick JP and Khatri P. Recanalization and Angiographic Reperfusion Are Both Associated with a Favorable Clinical Outcome in the IMS III Trial. *Interv Neurol*. 2016;5:118-122.

10. Campbell BC, Hill MD, Rubiera M, Menon BK, Demchuk A, Donnan GA, Roy D, Thornton J, Dorado L, Bonafe A, Levy EI, Diener HC, Hernandez-Perez M, Pereira VM, Blasco J, Quesada H, Rempel J, Jahan R, Davis SM, Stouch BC, Mitchell PJ, Jovin TG, Saver JL and Goyal M. Safety and Efficacy of Solitaire Stent Thrombectomy: Individual Patient Data Meta-Analysis of Randomized Trials. *Stroke*. 2016;47:798-806.

11. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millan M, Davis SM, Roy D, Thornton J, Roman LS, Ribo M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG and collaborators H. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723-31.

12. Muir KW, Ford GA, Messow CM, Ford I, Murray A, Clifton A, Brown MM, Madigan J, Lenthall R, Robertson F, Dixit A, Cloud GC, Wardlaw J, Freeman J, White P and Investigators P. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry*. 2017;88:38-44.

13. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, Guillemin F and investigators T. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol*. 2016;15:1138-47.

14. Volny O, Cimflova P and Szeder V. Inter-Rater Reliability for Thrombolysis in Cerebral Infarction with TIC1 2c Category. *J Stroke Cerebrovasc Dis*. 2017;26:992-994.

15. Tung EL, McTaggart RA, Baird GL, Yaghi S, Hemendinger M, Dibiasio EL, Hidlay DT, Tung GA and Jayaraman MV. Rethinking Thrombolysis in Cerebral Infarction 2b: Which Thrombolysis in Cerebral Infarction Scales Best Define Near Complete Recanalization in the Modern Thrombectomy Era? *Stroke*. 2017;48:2488-2493.

16. Kaesmacher J, Dobrocky T, Heldner MR, Bellwald S, Mosimann PJ, Mordasini P, Bigi S, Arnold M, Gralla J and Fischer U. Systematic review and meta-analysis on outcome differences among patients with TIC12b versus TIC13 reperfusion: success revisited. *J Neurol Neurosurg Psychiatry*. 2018.

17. Kaesmacher J, Maegerlein C, Zibold F, Wunderlich S, Zimmer C and Friedrich B. Improving mTIC12b reperfusion to mTIC12c/3 reperfusion: A retrospective observational study assessing technical feasibility, safety and clinical efficacy. *Eur Radiol*. 2018;28:274-282.

18. Dargazanli C, Consoli A, Barral M, Labreuche J, Redjem H, Ciccio G, Smajda S, Desilles JP, Taylor G, Preda C, Coskun O, Rodesch G, Piotin M, Blanc R and Lapergue B.

Impact of Modified TIC1 3 versus Modified TIC1 2b Reperfusion Score to Predict Good Outcome following Endovascular Therapy. *AJNR Am J Neuroradiol*. 2017;38:90-96.

19. Kleine JF, Wunderlich S, Zimmer C and Kaesmacher J. Time to redefine success? TIC1 3 versus TIC1 2b recanalization in middle cerebral artery occlusion treated with thrombectomy. *J Neurointerv Surg*. 2017;9:117-121.

20. Almekhlafi MA, Mishra S, Desai JA, Nambiar V, Volny O, Goel A, Eesa M, Demchuk AM, Menon BK and Goyal M. Not all "successful" angiographic reperfusion patients are an equal validation of a modified TIC1 scoring system. *Interv Neuroradiol*. 2014;20:21-7.

21. Fugate JE, Klunder AM and Kallmes DF. What is meant by "TIC1"? *AJNR Am J Neuroradiol*. 2013;34:1792-7.

22. Kallmes DF. TIC1: if you are not confused, then you are not paying attention. *AJNR Am J Neuroradiol*. 2012;33:975-6.

23. Tomsick TA, Carrozzella J, Foster L, Hill MD, von Kummer R, Goyal M, Demchuk AM, Khatri P, Palesch Y, Broderick JP, Yeatts SD, Liebeskind DS and Investigators II. Endovascular Therapy of M2 Occlusion in IMS III: Role of M2 Segment Definition and Location on Clinical and Revascularization Outcomes. *AJNR Am J Neuroradiol*. 2017;38:84-89.

24. Tomsick TA, Yeatts SD, Liebeskind DS, Carrozzella J, Foster L, Goyal M, von Kummer R, Hill MD, Demchuk AM, Jovin T, Yan B, Zaidat OO, Schonewille W, Engelter S, Martin R, Khatri P, Spilker J, Palesch YY, Broderick JP and Investigators II. Endovascular revascularization results in IMS III: intracranial ICA and M1 occlusions. *J Neurointerv Surg*. 2015;7:795-802.

25. King S, Khatri P, Carrozzella J, Spilker J, Broderick J, Hill M, Tomsick T, Ims and Investigators II. Anterior cerebral artery emboli in combined intravenous and intra-arterial rtPA

treatment of acute ischemic stroke in the IMS I and II trials. *AJNR Am J Neuroradiol*. 2007;28:1890-4.

26. Zaidat OO, Castonguay AC, Linfante I, Gupta R, Martin CO, Holloway WE, Mueller-Kronast N, English JD, Dabus G, Malisch TW, Marden FA, Bozorgchami H, Xavier A, Rai AT, Froehler MT, Badruddin A, Nguyen TN, Taqi MA, Abraham MG, Yoo AJ, Janardhan V, Shaltoni H, Novakovic R, Abou-Chebl A, Chen PR, Britz GW, Sun CJ, Bansal V, Kaushal R, Nanda A and Nogueira RG. First Pass Effect: A New Measure for Stroke Thrombectomy Devices. *Stroke*. 2018.

## Figure Legend

Figure 1. Angiography of final reperfusion of the MCA territory, revealing (A) eTICI 2b50=50-66% versus (B) eTICI 2b67 = 67-89%.

Figure 2. Angiography of final reperfusion of the MCA territory, revealing (A) eTICI 2c=90-99% versus (B) eTICI 3 = 100%.

Figure 3. Graphical depiction of mRS outcomes at 90 days based on eTICI grades for ICA occlusions (above) and M1 MCA occlusions (below).

Figure 4. ROC curves showing the predictive ability of various TICI grades with respect to clinical outcomes, using (A) mRS (0-1) and (B) mRS (0-2).

Table 1. Study population

| Characteristic                   | Mean ± SD (N)<br>Median (IQR)<br>or % (n/N) |
|----------------------------------|---------------------------------------------|
| Age (years)                      | 65.4 ± 13.5 (729) [67.0] (56.8, 76.0)       |
| Female sex                       | 47.5% (346/729)                             |
| NIHSS at baseline                | 17.1 ± 4.8 (725) [17.0] (14.0, 20.0)        |
| ASPECTS at baseline              | 7.6 ± 1.8 (722) [8.0] (7.0, 9.0)            |
| Collateral grade                 |                                             |
| 0                                | 0.9% (5/562)                                |
| 1                                | 13.7% (77/562)                              |
| 2                                | 44.3% (249/562)                             |
| 3                                | 41.1% (231/562)                             |
| tPA delivered                    | 85.7% (625/729)                             |
| Onset to randomization (min)     | 205.7 ± 96.9 (728) [184.5] (140.5, 246.3)   |
| Onset to arterial puncture (min) | 252.6 ± 96.8 (685) [240.0] (185.0, 300.0)   |
| eTICI category post-procedure    |                                             |
| 0                                | 8.2% (60/729)                               |
| 1                                | 2.6% (19/729)                               |
| 2a (0-49%)                       | 13.7% (100/729)                             |
| 2b50 (50-66%)                    | 14.1% (103/729)                             |
| 2b67 (67-89%)                    | 29.9% (218/729)                             |
| 2c                               | 22.8% (166/729)                             |
| 3                                | 8.6% (63/729)                               |

Table 2. Distinctions between eTICI categories with respect to clinical outcomes for all cases

| eTICI         | mRS 0<br>% (n/N) | mRS 1<br>% (n/N) | mRS 2<br>% (n/N) | mRS 3<br>% (n/N) | mRS 4<br>% (n/N) | mRS 5<br>% (n/N) | mRS 6<br>% (n/N) |
|---------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| 0             | 0.0% (0/59)      | 3.4% (2/59)      | 18.6% (11/59)    | 5.1% (3/59)      | 33.9% (20/59)    | 6.8% (4/59)      | 32.2% (19/59)    |
| 1             | 0.0% (0/19)      | 5.3% (1/19)      | 15.8% (3/19)     | 10.5% (2/19)     | 21.1% (4/19)     | 5.3% (1/19)      | 42.1% (8/19)     |
| 2a (0-49%)    | 10.0% (10/100)   | 6.0% (6/100)     | 13.0% (13/100)   | 14.0% (14/100)   | 25.0% (25/100)   | 10.0% (10/100)   | 22.0% (22/100)   |
| 2b50 (50-66%) | 4.9% (5/103)     | 16.5% (17/103)   | 25.2% (26/103)   | 14.6% (15/103)   | 18.4% (19/103)   | 7.8% (8/103)     | 12.6% (13/103)   |
| 2b67 (67-89%) | 13.3% (29/218)   | 21.1% (46/218)   | 17.9% (39/218)   | 23.4% (51/218)   | 10.1% (22/218)   | 5.0% (11/218)    | 9.2% (20/218)    |
| 2c            | 14.5% (24/165)   | 22.4% (37/165)   | 20.0% (33/165)   | 17.0% (28/165)   | 12.1% (20/165)   | 4.8% (8/165)     | 9.1% (15/165)    |
| 3             | 12.7% (8/63)     | 36.5% (23/63)    | 19.0% (12/63)    | 9.5% (6/63)      | 11.1% (7/63)     | 4.8% (3/63)      | 6.3% (4/63)      |

Table 3. Multivariable model of eTICI categories and clinical outcomes

Multivariable model: Ordinal logistic regression, outcome mRS (shift)

| Predictor                           | Common odds ratio | LCL  | UCL   | p-value |
|-------------------------------------|-------------------|------|-------|---------|
| Age (per year)                      | 0.96              | 0.95 | 0.97  | <0.001  |
| NIHSS at baseline (per point)       | 0.92              | 0.89 | 0.95  | <0.001  |
| Male gender (vs female)             | 1.16              | 0.89 | 1.52  | 0.270   |
| ASPECTS (per point)                 | 1.20              | 1.11 | 1.30  | <0.001  |
| Onset to randomization (per 60 min) | 0.89              | 0.82 | 0.98  | 0.017   |
| Occlusion location                  |                   |      |       |         |
| ICA (reference level)               | 1.00              | NA   | NA    | NA      |
| MCA                                 | 1.36              | 0.99 | 1.87  | 0.056   |
| tPA administered (vs no tPA)        | 1.02              | 0.66 | 1.56  | 0.938   |
| eTICI grade                         |                   |      |       |         |
| 0 (reference level)                 | 1.00              | NA   | NA    | NA      |
| 1                                   | 0.91              | 0.35 | 2.38  | 0.843   |
| 2a                                  | 1.43              | 0.78 | 2.64  | 0.251   |
| 2b50                                | 2.44              | 1.34 | 4.43  | 0.003   |
| 2b67                                | 5.11              | 2.93 | 8.91  | <0.001  |
| 2c                                  | 5.19              | 2.93 | 9.21  | <0.001  |
| 3                                   | 7.33              | 3.72 | 14.44 | <0.001  |

eTICI level adjacency comparisons by above adjusted multivariable analysis, outcome mRS (shift)

| Adjacency    | Common odds ratio | LCL  | UCL  | p-value      |
|--------------|-------------------|------|------|--------------|
| 2a vs 0/1    | 1.47              | 0.84 | 2.57 | 0.181        |
| 2b50 vs 2a   | 1.71              | 1.02 | 2.85 | <b>0.041</b> |
| 2b67 vs 2b50 | 2.10              | 1.36 | 3.22 | <b>0.001</b> |
| 2c vs 2b67   | 1.02              | 0.70 | 1.46 | 0.934        |
| 3 vs 2c      | 1.41              | 0.83 | 2.40 | 0.205        |



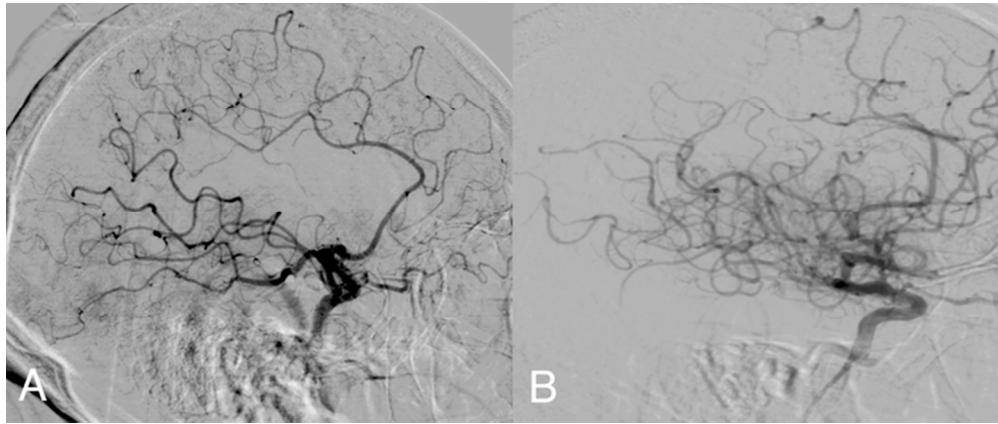


Figure 1. Angiography of final reperfusion of the MCA territory, revealing (A) eTICI 2b50=50-66% versus (B) eTICI 2b67 = 67-89%.

63x26mm (300 x 300 DPI)

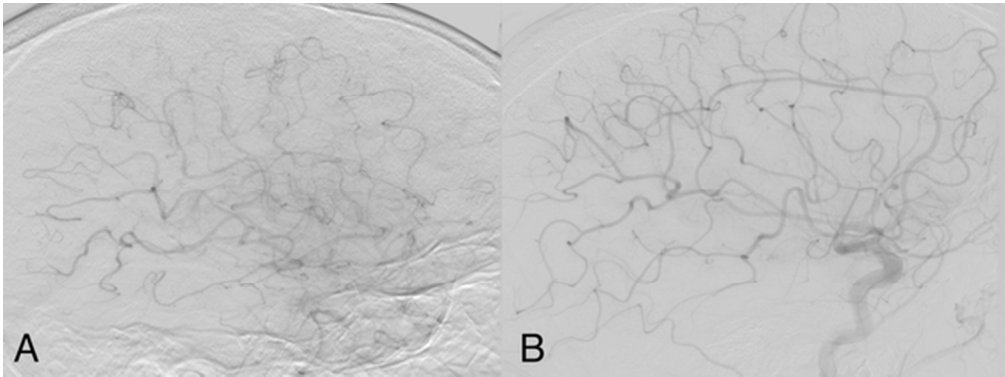
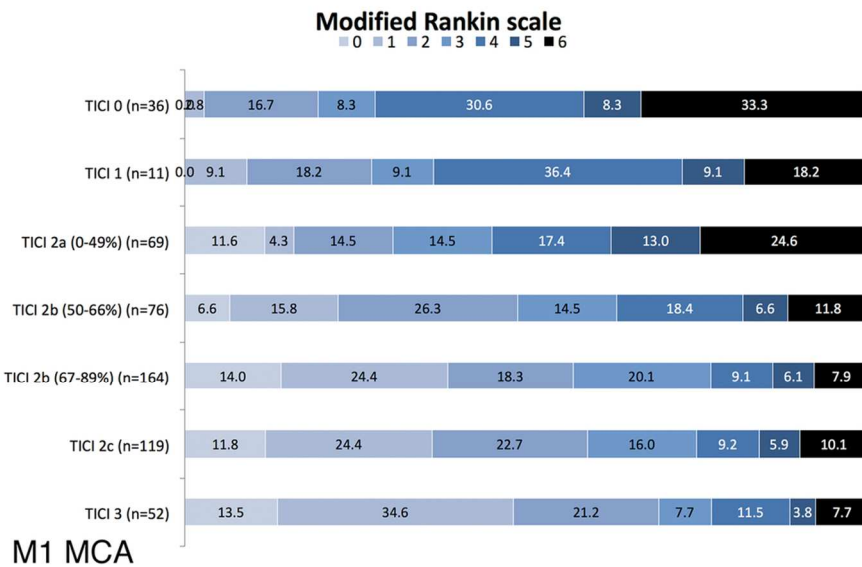
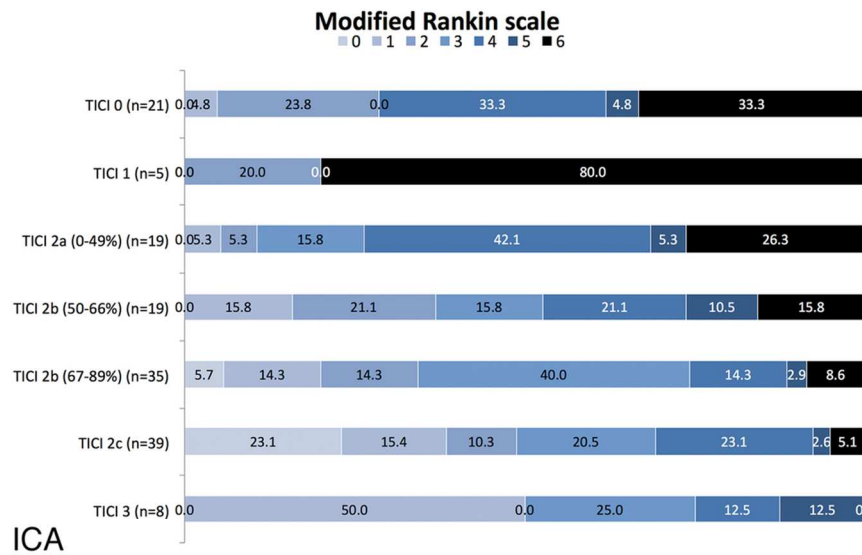


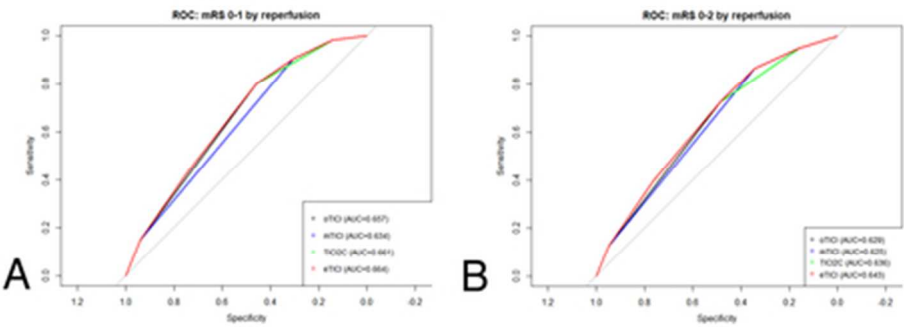
Figure 2. Angiography of final reperfusion of the MCA territory, revealing (A) eTICI 2c=90-99% versus (B) eTICI 3 = 100%.

56x21mm (300 x 300 DPI)



Graphical depiction of mRS outcomes at 90 days based on eTICI grades for ICA occlusions (above) and M1 MCA occlusions (below).

96x122mm (300 x 300 DPI)



ROC curves showing the predictive ability of various TICI grades with respect to clinical outcomes, using (A) mRS (0-1) and (B) mRS (0-2).

40x14mm (300 x 300 DPI)